Case Report

Treatment of Glucantim™- Resistant Cutaneous Leishmaniasis Using Combination Therapy of Allopurinol and Trichloroacetic Acid (TCA) 50%; Report of Three Cases

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Abstract

Background: There are 3 main forms of leishmaniasis—visceral, cutaneous, and mucocutaneous. Leishmania parasites are transmitted by the bite of infected female phlebotomine sand flies.

Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis and causes skin lesions, leaving life-long scars and serious disability. About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia. Over two thirds of new CL cases occur in 6 countries that Iran (Islamic Republic of) is one of them. An estimated 0.6 million to 1 million new cases occur worldwide annually.

If there is no remission with Glucantim as a choice of drug, other treatments such as cryotherapy and thermotherapy methods are used or other drugs such as allopurinol, pentamidine and amphoteracin are prescribed in this disease. The use of trichloroacetic acid (TCA) 50% solution is another effective treatment.

Case presentation: We report three cases (two women and one man) of cutaneous leishmaniasis resistant to Glucantim treated with combination therapy of allopurinol and TCA 50%.

Conclusion: According to the results, the use of combination therapy of allopurinol and TCA 50% could be used as one of the alternative treatments in Glucantim™- resistant cutaneous leishmaniasis.

ABBREVIATIONS

TCA: Trichloroacetic Acid

INTRODUCTION

There are 3 main forms of leishmaniasis—visceral, cutaneous, and mucocutaneous. Leishmania parasites are transmitted by the bite of infected female phlebotomine sandflies [1]. The life cycle of Leishmania changes between two morphological forms: intracellular amastigotes in the mammalian host and promastigotes in the sand fly vector [2].

Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis and causes skin lesions, leaving life-long scars and serious disability. About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia. Over two thirds of new CL cases occur in 6 countries that Iran (Islamic Republic of) is one of them. An estimated 0.6 million to 1 million new cases occur worldwide annually.

Leishmaniasis transmission occurs in a complex biological system involving the human host, parasite, sand fly vector and in some causes an animal reservoir host, prevention and control of leishmaniasis requires a combination of strategies [1]. Cutaneous leishmaniasis has a high prevalence in Iran. A total of 37,001 cases of the disease were reported from 2012 to 2013, indicating 25 in 100,000 prevalence with 72% of the cases living in endemic areas [3]. The treatment-resistant nature of the parasite is not yet thoroughly examined. Some strains of Leishmania parasites are inherently resistant to treatment [4,5].

Some studies have attributed this medication-resistance to the pharmacokinetic differences between medications or immune system differences in patients, while others blame the use of insufficient or repeated doses of medications for the failure in treatment and the emergence of in-vitro resistance [4-6]. If the disease is not treated using the select medication (Antimony compounds), other treatments such as cryotherapy and thermotherapy or medications such as Allopurinol, Pentamidine and Amphotericin are administered instead [7]. The use of Trichloroacetic acid (TCA) solution (another treatment option) as a chemical and superficial peeling is a traditional and popular method for skin rejuvenation [8]. Higher TCA concentrations will penetrate to the mid-reticular dermis [9]. TCA peeling induces the skin stress response system resulting in reconstitution of the epidermis and dermis through wound healing processes thus, TCA peeling could be as a potential therapeutic option for cutaneous leishmaniasis [10-12]. Oral allopurinol is a cheap and affordable alternative treatment that affects different in-vitro strains of the parasite and is recommended to be used due to its easy route of administration [13]. Allopurinol destroys the parasite by disrupting the synthesis of vital nucleotides and inhibiting purine bases, which are essential to the survival of the parasite [14,15]. In a hyper-endemic region like Isfahan, the administration of allopurinol with glucantime was found to have a stronger effect compared to only glucantime on the treatment of Leishmania major infection, and the dosage of glucantime can even be reduced to half with this combination [16]. According to studies, the use of TCA 50% alone or in combination with glucantime has been significantly effective in the treatment of patients. Studies conducted at different times and with different methodologies have unanimously confirmed the effectiveness of TCA 50% for treatment [17,18]. A study conducted on a case of lipid leishmaniasis found that topical treatment with TCA 50% is highly effective [17]. In the present study, three patients lived in hyper endemic area of leishmania major with positive direct smear (Leishman body was observed by microscopic examination). Patients did not respond to glucantime treatment were treated with a combination of allopurinol and TCA 50% (Figure 1).

**CASE PRESENTATION**

**The First case**

The first case was a 39 year-old woman residing in the leishmaniasis-endemic suburbs of Isfahan. The disease had developed one month and a half before the experiment in the patient. Upon admission, the lesion was in the form of an indurate erythematous nodule on the big toe that was 0.5 × 1 centimeter in size. Treatment began with TCA 50% solution. The patient’s second visit (one week) did not show any improvements and the size of the lesion had increased. Treatment then began with systemic glucantime (megluminantimoniate, Aventis France) injection. Despite a relative improvement after five injections, the patient showed sensitivity to the medication and this treatment was terminated. Treatment began once again with TCA 50% solution. Due to the absence of improvements in the fourth week’s visit, treatment was continued with TCA 50% solution. The patient still showed no improvements in the fifth week’s visit and treatment was again continued with TCA 50%. In the sixth week’s visit, two new nodules had appeared on the right foot and an antibiotic treatment began with Azithromycin and Fluconazole along with TCA 50%. In the seventh week’s visit, the patient still showed no improvements and a sporotrichoid form was also observed. Treatment with allopurinol thus began at 15 mg per kg of body weight and lasted for six weeks alongside TCA 50% solution (administered topically once a week with a swap until a 1-mm radius of the lesion was white). In the eighth week’s visit, i.e. the first week after beginning treatment with allopurinol, the patient showed a relative improvement. The sporotrichoid form had disappeared and in duration was decreased. In the ninth week’s visit, i.e. two weeks after beginning treatment with allopurinol, a complete recovery was observed.

**The Second case**

The second case was a 36 year-old man residing in Isfahan infected at Shahid Beheshti Airport in Isfahan. His disease had begun five months before his admission. In the first visit, the researcher found that the patient had received 40 glucantime injections before visiting the center and since no improvements had been observed, treatment with Fluconazole and Azithromycin had also began in him but in vain. At the time of the first visit, the patient had a lesion of 5 x 6 cm in size in the form of an erythematous plaque on the right arm with satellite nodules and a sporotrichoid form and an indurate plaque. Treatment began with TCA 50% solution. The patient showed no improvements when visited in the second week. Treatment with allopurinol then began at 15 mg per kg of body weight and lasted for six weeks along with TCA 50% solution. In the third week, a relative improvement was observed with a smaller-sized lesion and treatment was thus continued. In the fourth week, a relative improvement was once again observed with a smaller-sized lesion and the disappearance of the sporotrichoid form and in duration was decreased. The patient was advised to continue the treatment; he came back two weeks later with no in duration and a full recovery (Figure 2,3).

**The Third case**

The third case was a 60 year-old woman residing in Varzaneh, Isfahan, and infected in the same city. Her disease had begun six months before her admission. Upon admission, the patient had an erysipeloid lesion with an indurate plaque on his nose. Prior to this visit, she had received 40 glucantime injections along with
antibiotics. Despite these treatments, the primary lesion, which was in the form of a plaque, had grown in size and turned into an erysipeloid. Treatment with allopurinol then began at 15 mg per kg of body weight and was continued for six weeks along with TCA 50% solution. One week after the treatment, a relative improvement was observed and the lesion had reduced in size. Treatment then continued and the patient was visited again two weeks later. This time, the lesion was even smaller and the in duration was decreased. Treatment continued until the patient returned fully-recovered three weeks later (Figure 4,5).

The consent form was given from all of patients. The patients followed after six months of treatment and parasitological examination were negative.

DISCUSSION

Cutaneous leishmaniasis is a disease that goes away on its own within six months to a year (depending on its type) in 90% of the cases. Despite its spontaneous treatment, the scar left on the body by the disease can create many social and psychological problems for the patients. Secondary infection is one of the problems that we encounter in the long lasting cases which increase remaining scars. Administering allopurinol has been a common practice in the treatment of this disease for many years. When combined, allopurinol and antimony compounds have been very effective in the treatment of this disease. A study of the effect of allopurinol and stibogluconate showed that the use of stibogluconate alone leads to a 39% improvement while its combined use with allopurinol causes up to 71% improvement [16]. Another study on the effect of the combined use of allopurinol and meglumine antimony showed that the combined effect of these two medications is far greater than the effect of administering glucantime alone (P=0.05); [19]. Another study conducted to investigate the effect of the combined use of allopurinol and meglumine at a lower dosage showed that the low-dose administration of these two medications has much stronger effects on Leishmania major than when a high dose of meglumine antimony is administered by itself (P=0.05); [20]. A study conducted on the effect of allopurinol on glucantime-resistant *Leishmania tropica* promastigotes also showed that the mechanisms of glucantime resistance lead to morphologic changes and increases the growth rate of promastigotes while allopurinol reduces the number and growth percentage of both the resistant and primary types of *Leishmania tropica* parasites. Nonetheless, the sensitivity of in-vitro resistant *Leishmania tropica* parasites (promastigotes) to allopurinol is reportedly higher than that of the primary (non-resistant) type.

According to the present findings, allopurinol is an affordable oral medication recommended to be used for the treatment of...
primary Leishmania major; however, it is not recommended to be used alone for the treatment of the resistant types of the disease [21]. TCA 50% is commonly used as a skin-peeling medication [18]. The combined use of TCA 50% and other medications has produced very good results in the treatment of leishmaniasis. TCA 50% is likely effective due to its penetration of the epidermis, dermis and the parasite-containing macrophage infiltration locus and also due to possible eradicating effects on the parasite or its sources of nutrition. Stimulating the production of collagen and reducing the appearance of scars are other reasons for the use of topical TCA 50% in the treatment of leishmaniasis. In another study, Sadeghian et al. administered TCA 50% with systemic glucantime to one patient for the treatment of lipoid leishmaniasis and observed a significant improvement; in their one-year follow-up of the patient, no detectible scars were observed on the patient’s face [17]. Another study conducted on the effect of TCA 50% compared to topical glucantime injection reported a similar effectiveness for both treatments (P<0.05); [18].

The present study examined the effect of combined treatment with allopurinol and TCA 50% on three cases resistant to glucantime. According to the findings, the combined use of these two medications is recommended as a treatment of choice for glucantime-resistant cases and as an alternative treatment for non-resistant patients, especially in cases where there is no access to glucantime.

REFERENCES

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